β Group

Sana'a University

دفعة 33 طب بشري

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Lectures

ANS
GIT

A PLUS
No pain. No gain

رشاد الحيفاني

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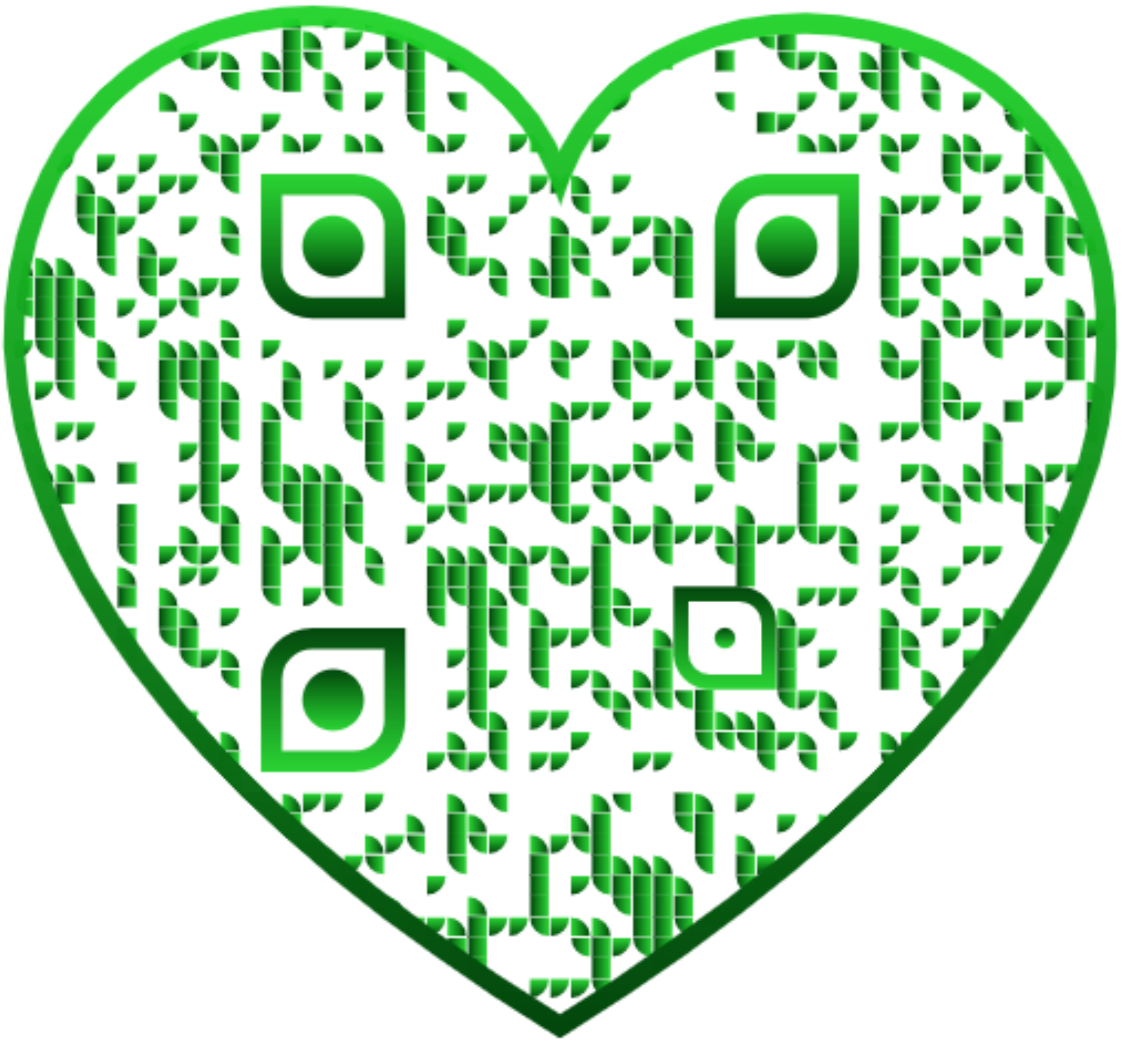


- ANS :- it's the divisson of the nerves sys. concerned with regulation of autonomic functions.
- It's divisions :- a) sympathatic b) parasympathatic
- system :- 1. higher center 2- Nerves 3-chemical transmitters 4-Receptor
* High centers :- a) Medulla b) hypothalamus c) Retrcular formation d) Cortex
# Most internal organs are "dual supply" [sympathatic & parasympathatic]
# Autonomic nerve supply relay to (ganglia) : collection of neurons ! ganglia → control:(+ or - the signals)
# In parasympathatic the ganglia ⇒ close to organ
# In sympathatic " " ⇒ paravertebral
# The drugs may works in :- ① nerve ending ($\underline{s}$ or $\underline{p}$) ② Receptors ③ parasympathatic ganglia
→ Most organs receive dual supply : in some case one of them takes the overhand from the other or they may equalize e.g : (sym : 50 - para 50), (sym. : 80 - para : 20), etc.
→ Some Organs receive single supply as :- ① suprarenal gland ② sweet gland ③ B.Vs
The organs dose not have all types of receptors but mostly there are One receptor " pre-dominant "
MAchR :- The fastest receptor that can responce to ACh.
Cholinergic receptors :- M receptors : $M_{1,2,3}$
Adrenergic receptors :- α_1, α_2, B_1, B_2, B_3
More than 99% of the receptors presnce inside the heart :- B_1

⇒ Bradycardia (para..)	⇒ Tachycardia (sym.)
## :. Block M2 receptor	## :. Block B_1 receptor
. activate B receptor	. activate M2 receptor

Q :- How can we control the Autonomic system ?
1- higher center 2-Nerve ending 3- Receptor (more selective)
* ganglion blockers اكتر حاجة بتأثر على ganglia لأنها non-selective = non-specific يعني
Fate of transmitter :- breakdown by cholinesterase enz. (ChE)
⇒ ChE :- 1) true (acetyl ChE) → specific (just breaks Ach)
2) pseudo (butyl ChE) → non-specific (breaks Ach + heroin cocaine, ... etc. [its presence in Liver, plasma]
⇒ true :- CNS, RBCs + essential for Life unlike pseudo

• Fate of chatecholamine (epinephrine + nor-epinephrine) :- reuptake 80 % & 20 % → breaks by MAO enz. + COMT

Reserpine drug :- MoA :-
يمنع الـ NA من الدخول إلى vessels وبالتالي يتراكم في السيتوبلازم ويتكسر بواسطة MAO & COMT enz. إلى :- ① metanephrine ② VMA وتخرج في البول

→ Normal ring of catecholamine in the blood :- 10 ng/L
* the stress ↑ this ring (x10) ⇒ 100 ng/L.
* Adrenaline ampule (inj.) ⇒ ↑ the ring to 100 ng/L
* phenochromocytoma (suprarenal gland tumor)

phenochromocytoma :- unilateral tumor [in 90 % of cases it's penign] & it's origin ⇒ anterochromatine cells.

nAch receptors :- a) neural → ganglia b) muscular → muscles
(a + b) are Ion channel, they differ from the other receptors in the tissue (N_1, N_2, N_3) in structure & function.

The 3rd division of ANS is :- ENS of intestine ★(mcq)

⇒ NANC (non-adrenergic non-cholinergic) transmitters :- ATp - purines
Angiotensin - histamine - serotonin - No - etc -
it's receptors → regulation function to 1ry transmitter (Ach)

✳ Adrenergic receptors :-
كل الـ adrenergic receptor - يتسمى receptors وتجد أن غالبية الـ Gprotien يعني
تنقسم Gprotien بنسبة 70 %، له ثلاثة أنواع :-
1- stimulatory 2- Inhibitory 3- Gq

Types of adrenergic receptors :-

① α_1 :- (ABC) subdivide
a - Blood vessels :- if st. → V.C [Precisely $\alpha_1 A$]
b - Uterus :- contraction ★ لكن ليس لدرجة أن يسبب إجهاض "apportion"
c - eye :- mydriasis (α_1)
d - Urinary & GIT :-
1- wall → relaxation 2- sphincter → contraction ($\alpha_1 A$ & $\alpha_1 D$)
e - Sweat gland :- In for head & palm

α_2 :- ABC subdivide

- mostly in presynaptic (nerve terminal)
- nerve terminal regulation
- α_2 always opposite α_1 and it's always inhibitory ↓ NA

B_1 :- Cardiac B_1 :-

1- ↑ all cardiac properties : HR, Contractility, ... etc
* إذا جاء المريض وكان يشتكي من خفقة في النبض أو Tachycardia ممكن يكون السبب هو B_1 والحل الأنسب هو أن نعطي B_1 blockers
2- Kidney : secreat Renin
3- Lypocyte ↔ adepocyte { overhand لكن بكميات قليلة لأن الـ B_3 سنذكره لاحقاً في الـ }

B_2 :-

- في حالة الخطر تساعد على الهروب وأثناء الجري نحتاج لـ :- ① SK.m : تقوم الـ B_2 بفعل V.D للـ skin vessels حتى يكثر الدم في العضلة ويسهل ذلك عملية الجري وآلية ذلك كالتالي :- B_2 تحفز إستجابة الـ nAchR للـ Ach بشكل أفضل من المعتاد أي أنها تقوم بفعل facilitation في الـ neuro muscular transmittion
← أيضاً تقوم B_2 بإدخال K^+ إلى العضلات ← action potential وهذا يسبب إنقباض العضلات بسهولة ودون أية مشاكل لكن خلال ذلك يحدث نقص في نسبة الـ K في الدم ← hypokalemia (SE)

Shortly :-

1- V.D of sk.m (blood vessels).
2- Facilitation of neuromuscular transmittion.
3- ↑ the storage of K^+ inside the muscle from the blood.
4- ↑ glucose in Blood from the Liver.
5- Bronchodilatation.
6- Secreat aqueous humour.
7- Relaxation of uterus during dangrous to avoid apportion.

N.B ← تقريباً كل وظائف B_2 مفيده عدا شيء واحد أنها ممكن أن تسبب Tremors أثناء قيامها بالـ facilitation

B_3 :-

← نستطيع القول بأن B_3 هي نوع من B_2 !! وهي موجودة بشكل كبير في الـ adipose tissue وإذا اشتغلت ← Lipolysis

N.B :- لا يوجد B_3 agonist because it dosn't uniformally distriputed all over the body.

Adrenergic receptor :-

- أي دواء يحفز ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$) تسميه : Sympathomimatic سواء
قام بتنبيه جميعها بشكل كامل أو بعض منها فقط ...

Sympathomimatic :-

1- MOA :- [a] Direct :- * اذا كان الدواء ينبه الـ α في الـ n. ending
بشكل مباشر تسميه Direct sympathomimatic

[b] Indirect :- * إذا كان عمله : release for NA from n. ending أو أنه قام بتثبيط الـ MAO enz.
تسميه Indirect sympathomimatic

* Chemical :-

[A] Catecholamine :- 1- not absorped orally 2- Can pass BBB
3- MAO & COMT 4- short duration

[B] Noncatecholamine.

* Drugs :-

# prototybe :- the most important drug of all familly is :-
Adrenaline = (Epinephrine) :-

- it's the chemical transmitter inside the sympathetic sys.
- Origin :- suprarenal gland → (natural)

→ Chemical :-

1- Natural catecholamine 2. Contain catechol ring.

⇒ pharmacokinetics :-

a- absorption :- ① not orally absorption ② Skin absorption slugish "few → VC
③ opthalmic absorption (could be but rare) ④ Inhalation

b- Distnpution :- ① Can pass BBB so it dosn't reach to CNS

c- Metabolism :- يتكسر بواسطة الـ MAO & COMT enz. ويتم ذلك خلال دقائق

d- Excretion :- a) metanephrine b) VMA

حُقنة الأدرينالين تؤخذ SC أو عضلة IM وفي حالات IV لكن هنالك خطر كبير لأنها قد تسبب مشاكل في القلب ← Ventricular fibrillation

* MOA :-

* تأثير الـ adrenaline بتشاور على الـ receptors بتاعة الـ α_2 !! لأن الـ presynaptic " لأنه " بيستقبل الوصول إليها أيونات زيادة بتأثر كافية للوصول لمنطقة الـ (presynaptic) .

$\alpha_1 \rightarrow Gq \rightarrow IP_3 \rightarrow Ca^{++}$

$\beta \rightarrow \uparrow cAMP \rightarrow$ activates "protien kinase" } "molecular mechanism"

س/ ماهي آلية عمل الـ adrenaline !!

* Effects :-

[1] Blood pressure :- according to dose !!

→ Ampule or ½ → ↑ systole , ↓ diastole

→ more than therapetic dose :- (large dose) :- ↑ systole , ↑ diastole *why?

* because α (predominate) → generLize the V.C → ↑ diastolic Bp .

[2] Heart :- ① ↑ HR ↑ contractility ② arrthmia (VF)

[3] bronchi → β_2 → Bronchodilatation

[4] CNS → No effect because it don't pass BBB !

[5] eye → β_2 → secreat aqueous humour .in case of Glucoma .

* Uses :- in emergency :-

[1] Acute anaphelatic chock * the best rout of administration of Ad. in case of Anaphlactic chock ? I.M

[2] Acute bronchospasm .

[3] Cardiac arriest .

[4] Local anasthesia → V.C → ↓ Bleeding + long duration of local anasthesia ...

* SE :-

1- ↑↑↑ hypertension → cerebral hemorrhage
2- Tremors
3- Tachycardia → arrhythmia → V.F
4- Acute heart failure
5- " pulmonary edema
6- gangrene of fingers.

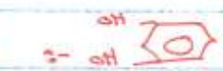
Q:- The most dangrous adverse effect of epinephrine injection is?
arrhythmia & V.f

* Contraindication :-

1- Hypertension
2- Cardiovascular problems
3- Large dose with Local anasthesia
4- Cardiac outflow obstruction (Coo)
5- thyperthyroidism (sympathetic over activity)

Direct acting sympathomimatics

2- NA 3- Dopamine 4- B_2 agonist → selective / → non-selective 5- Daputamine
6- α agonist 7- Dopamine receptor agonist ...

2 NA :-  :-

1- catecholamine 2- not absorped orally 3- does not pass BBB
4- Not exposure to air

→ NA :-

[α_1, α_2, α_3] but 90% ⇒ (α_1) ⇒ V.C → the main effect of epinephrine vc.

- B_1 :- 10% ⇒ NA when given → α_1, B_1

- very short acting

Uses :-

1- V.C (acute hypotension state) !

2- we don't gave it injection direct, SC, Orally → The only route is :- intravenous infusion ! Q :- why ?

→ answer :- VC → tissue necrosis !!

↑Bp ← لازم نقيس الضغط للمريض أثناء إعطاء الدواء ذيه !! لأنها ممكن تسبب

* cerebral hemorrhage * ← مجلطة وجدة شديدة

3- Baro reflex → (vagus n.) :-

reflex bradycardia ← الضغط مجلطة لازم يترسل إلى الدماغ ويقوم يقل ↑↑ أي سبب

→ Atropine :- stop this reflex !

[3] Dopamine :-

Tyrosin → Dopa → Dopamine → NA → A

→ Dopamine :- (Ampule) :- it's differ from the NA, A

dose يستقل ! جيب على حسب الـ « Dopamine » هو إلي الـ ← !!

[1] Low dose ⇒ D_1 :- in renal vasculature → ↑ urine output.
mesentric B.v

[2] Intermediate dose → B_1 → Cop ↑

[3] high dose → α_1 → V.C → ↑↑ Bp.

Shock :- ↓↓ Bp ، tissue perfussion :-

Q :- with shocked pt., what's your goal of therapy ?

A: shocked state means : hypotension associated with impairement of tissue perfussion ⇒ my goal of therapy is : to restore perfussion first then hypotension ..

[4] Dobutamine :-

- Dopamine	- Dobutamine
- Not Catecholamine, comes from : DopA	- Synth. Cat.
- $D_1 > B_1 > \alpha_1$	- B_1 only
- Shock : syptic_chock (specially)	- ↑HR, Cop
	- Shock : Cardiogenic

* B_2 agonists :- B

a) B_2 :- Selective B_2 agonist :-

B_1 :- Dubutamine ⇓ Cardiogenic chock !

B_1, B_2 " non-selective "

#Drugs :-

1- Salbutamol
2- Ritodrine
3- Turbutamine
4- Salmetrol
5- Formotrol
6- Bumbetrol

* non-catecholamine :-
- it could be given orally
- absorped - pass BBB
- Long duration
- doesn't distrared by MAO & COMT

* effects :-
1) B.Vs :- V.D in Sk.m & Coronary a.
2) Uterus : Relaxation
3) Tremors of the hand
4) Lung → bronchodilatation

* Uses :
~~- Bronchodilatation~~
1- Bronchial asthma
2- Utrine relaxation during pregnancy → Retrodrine

*Adverse effect :-
T → Tachycardia + arrhythmia
T → Tremors
T → Tolerance
H → Hypokalemia

" * #α_1 or α_2 : الأدوية إلي أتكلم عنها "

[1] Alpha agonist :- *phenylephrine *methoxamine *midodrine :-
-a- non-catecholamine drugs ... etc.
-b- Relativelly long duration (stim. of α_1 → V.C)
-c- use them when we want to ↑ Bp + VC
-d- eye drops, injection, nasal drops

[2] Xylometazoline , oxymetazoline :-

→ non selective (stim. α_1 (α_2)

!! α_2 ← لا يظهر تأثيرها إلا إذا استخدمنا دواء متخصص فيها

Nasal decongestant + eye drop -: لها V.C ← α_1 ← وأكثر إستخدام

* Adverse effects :-

[1] precutions of nasal decongestant :-

- Rebount (minimal dose)
- V.C ↑↑ systemic hypertension → stroke
- V.C → Atrophic Rhinatis ≈ mucosa ← لا تُستخدم لفترة أطول من ٣ أسابيع ...

(α_2 agonist) :-

[1] Clonidine :-

- stim. α_2 → ① ↓ central sympathatic outflow → ↓ Bp
  ② ↓ RBF (Renal blood flow) ③ ↓ GFR
  ④ drug addiction (أفيون)

* Adverse effect (SE) :-

- S → sedation , dry mouth
- S → Sudden with drual
- S → Sever hypertensive
- S → salt & water retention

[2] Tizanidine :-

① - stim α_2 in spinal cord just ⊥ ⟹ muscle relaxation
* use it in «Muscle spasm»

② ~ lultrible Sclerosis :- * (مرض تصلب متعدد)

Q: Drug use to relax the stim in painful static conditions?
⇒ Tizanidine .

[3] ⇒ fenol - dopam :-

1- catecholamine (synthetic) 2- Not absorped orally
3- don't pass BBB 4- must given parentral
5- Short duration 6- stim. D_1 just
7- Used as I.V injection in emergency cases

* SE :- ↑ Iop

glucoma. ← (↑Iop) بـ، systemic ← (↓Bp) هذا الدواء

Sympathomimatic drugs :-

A. Direct :-

1) Amphetamine :-

- indirect acting sympathomimatic drug
- synthetic (not natural) , non-catecholamine , can pass BBB +CNS

* SE :-

1- CNS ++ 2. Anorexia 3. euphoria
4- Hallucination 5. Addiction

* Contra indecation :-

1) CNS stimulant 2) obesity

تم منع هذا الدواء من السوق وإعتباره نوع من أنواع المخدرات

* Derevative drugs :-

1- Methyl phenidet ⇒ Modafinel
use in "ADHD" "Narcolepsy"

* SE :- *in high dose*

1- insomnia 2- tachycardia 3- nervesis 4- headach
5. segure → (dangrous for pt. with epilepsy disease)
6- physical dependance →

2- Cocaine : - alkaloid nature → coca plant !
- It has same effects of : amphetamine ★
- Local anesthetic "eye drop"
- If toxicity → adverse effect same to amphetamine
- we gave this pt. ⇒ Benzodyazpine

→ Mixed acting sympathomimtic :- * Ephedrine *
→ Direct : B , α
→ Indirect : Releas for NA
[use very minimal]

- alkaloid (natural)
- Non-catecholamine

1) Stim. all receptors α , B
2) Release NA from the Nerve ending
3) CNS +++

ممكن يستخدم على أساس أنه يقوم بتحفيز B_2 في حالة Bronchial asthma (BD) لأنه يحفز B_2 فيعمل لنا

ممكن يستخدم أيضاً لعلاج التبول اللاإرادي عند الأطفال

س/ لماذا لم يُعد دواء الـ ephidrine يستخدم ؟!

because it's :- ① non-selective sympathomimtic + mixed
② Urine Retention (specially in enlargmat prost)

س/ لماذا لا يؤخذ orally ويستخدم حقناً ؟ لأنه يؤثر على α، β receptors وينتج Contraction ← sphincter وفي الـ Relaxation ← الـ bladder وبالتالي يسبب احتباس للبول

س/ Adrenaline يحتوي α، β لماذا لم نقل أنه يسبب هذه الأعراض ؟
ج/ لأن بقائه في الجسم يستمر لدقائق فقط !

→ Alpha adrenergic blockers

Barorefflexes :-

Note : • sudden rise of Bp → RB "reflex bradycardia"
• " drop of Bp → RT "reflex tachycardia"

إذا لاحظنا أن الدواء هو المتسبب في sudden change ± يكون له تأثير على القلب
مثلاً :- Stim. β receptor .. ، الـ reflexes هذه لا تظهر.

Bradycardia يسبب Adrenaline * الأدرينالين

* س/ β blocker ← Bp ↓ هل تتسبب بـ RT ؟!
ج/ لا ، لأن الضغط عندما ينخفض تقوم الـ Strech receptor بإرسال إشارة على brain حتى تقوم بعمل (RT) وتذهب هذه الإشارة من الـ brain لكن وجود β blocker تكون مقفلة الـ receptor فلا يحدث (RT) !!

* α adrenergic adreno blockers :- 4 familles :-

① $\alpha_1 + \alpha_2$ (non-selective) : phenoxybenzamine / phentolamine
② α_1 (Selective α_1 blockers) : prazocine
③ α_2 (" α_2 ") : yohimbine
④ Ergotalkalout

Drugs :-

-1- phenoxybenzamine :-

• long duration • block $\alpha_1 - \alpha_2$ (irreversible)
• it takes (4 days) يجلس قافل الـ receptors مدة 4 أيام
يسبب hypotension لأنه يقفل الـ α ولما تنفتح هذه تسبب منع الـ VC ← Bressure ↓ ← Reflex Tachycardia ، وهذا من عيوب هذا الدواء :- Bp + RT

Uses of phenoxybenzamine :- long duration *

1- phenochromocytoma ⇒ tumor in the supra renal gland :-

* it's usually unilateral , benign , cause : ↑↑↑ Adrenaline secretion
* Increas "Adrenaline" in the blood :- a) pulpetation b) Tachycardia c) arrhythmia ... etc.

Treatment :- 1) surgical 2) Block $\alpha_{(1,2)}$, $\beta_{(1,2)}$ together

★ لايجب إعطاء أدوية α لمرضى حالة الـ phenochromocytoma لأننا بذلك سنلغي فعلنا الـ α فقط فتقوم الـ β بفعل تأثيراتها الجانبية مثل الـ Tachycardia, Tremors, arrhythmia بذلك نحن لحالة تفعلي α + دواء آخر "propranolol" لأنه يُعتبر $\beta_{blocker}$ يقفل على β_1 , β_2 مع بعضهما..

س/ هل نعطي أدوية β بمفردها ؟ ولماذا ؟!

ج/ لا ، لأن الـ α تقفل "severe V.C" وقد يسبب Cerebral hemorrhage

س/ عند إعطاء أدوية (α & β) مع بعضهما ، تكون الأولوية لمن ؟

ج/ يجب أن يتناول المريض أدوية $\alpha_{blocker}$ أولاً ، لأن المشكلة الرئيسية التي نرغب بعلاجها هي الـ hypertension ، فنبدأ بالأدوية التي تؤمن هذه المشكلة ثم $\beta_{blockers}$.

Adverse effects :-

1- ↓ Bp + RT 2- Failure of ejaculation 3- myosis

Selective α_1 blockers :-

1) prazosin :- • Doxasocine • Tamclocin • indoramine

→ it's blocks α_1 just receptor على الـ smooth muscle يفعل direct relaxation

→ no V.C ⇒ ↓Bp

- الدواء يتنافس مع أي تأثير مباشر ليس له علاقة بالـ α receptor على الـ smooth muscle يفعل V.C

← لأن الدواء عمل V.C بطريقتين ⇒ 1/ قفل α receptor ومنع الـ V.C 2/ رخّى الـ smooth muscle وعمل direct relaxation .

* any α_{blocer} cause → ↓Bp , RT (weak) because :-

a- non-selective : Tachycardia → + reflex (under effect of ↑ NA)

b- selective : ↓ Bp , RT but no ↑ (NA) ⇒ Tachycardia (weak)

shortly :-

① ↓ Bp with no RT.

② ↓ Bp with no effect on RBF, GFR.

③ ↓ Bp , ↓ Fat in blood.

[2] Doxasin :-

→ The longest drug with (duration of action) about 22 h. * (mcq)

* Uses :-

1- hypotension (specially with pt. with Kidney problems)
2- Acute heart farlure 3- enlargment prostate

Selective α_1 blocker :- ⇒ arterialar dilatetion → ↓ venous return

Tamsulosin → selective on (prostate) : it blocks α_{1A}, α_{1D} ⇒ +flow of urine without any change for Bp.

Adverse effect :-

1- first dose syncope :- مع أول جرعة يتناولها المريض ينخفض الضغط بشكل كبير
(salt & water depletion) : ويحدث ذلك فجأة لذلك قد يغشى على المريض ويحدث له
ويظهر التأثير خلال ٦٠ دقيقة ، لذلك نطلب من المريض أخذ جرعة صغيرة (بالقرص) ونزيد جرعة كل يوم

2- Fluid retension

3- Fulse +ve test for antinuclear factor قد يحدث خطأ ونظن أن
عند المريض *Romatoid arthraitis* (RA)

yohimbine :

- alkaloid (plants) - blocks α_2 - NA ↑ release

✳ Ergot alkaloids :

- Ergotamine - Ergonetrine - Ergotoxine (very toxic)

* Semisynthetic :

1 → Dihydroergot (H group)
2 → Methyl ergometrine (CH3 group)
3 → dihydroergotoxin
4 → Bromocryptine

semi synthetic

* They all stim. vomiting cinter
* Caffein → ↑ absorption for these drugs.

Ergotamine	partial agonist (α, 5HT)	V.C in cerebral B.vs	megrain
Ergometrine	agonist α_1	V.C on vessele + spasm on uterus	- ppH تزيف بعد الولادة
Dihydro-ergotoxine	antagonist blocks α	C.V.D cerebral B.vs	- cerebral insufficiency
Bromocryptine	① weak on α_1: (agonist & antagonist) من حيث أنه	② stim. D receptor	

* صداع نصفي

* Ergotamine : acute migraine attack

sudden release 5HT الأرغوت يعيد الـ B₂ إلى حالتها الطبيعية يقوم بحدث لنا

accumulation of waast products : وهذا يعمل VC for cerebral vessels وهذا يعمل

headach في severe VD تعمل لنا ← (waast metaboli products)

يُعتبر إنه الدواء الوحيد الذي يستطيع إعادة الـ vessels إلى حالتها الطبيعية

يفضل أخذ الدواء مع القهوة حتى تزيد من كفاءة امتصاصه

لا نستخدم هذا الدواء كـ إجراء وقائي للصداع ، لأنه سيسبب الصداع للشخص :-

Sudden release for 5HT يذهب الدواء لـ vessels يقوم بعمل VC وهذه الآلية تشابه آلية الـ

« headach » وبسبب الـ waast metaboli products يقوم الدواء بتجميع الـ

Tryptane :-

[symatreptan - Zolmetreptan - Naratreptan] ⇒ [expensive]

هذه العائلة تروح تشتغل على specific receptors في الدماغ مثل :-

[5HT receptor type 1D, 1B]

↓ releas of inflammatory mediator : عندما يشتغل الـ drug على هذه المستقبلات يسبب

والـ metabolic يلي بتظل وتعمل VD تشتغل وبالتالي الـ pain يعمل على mediator

لا تستطيع الخروج وبالتالي يذهب الألم ، عندما يمسك الـ drug يقوم بعمل VC B₁ ب

وبالتالي تعود الـ vessels إلى حالتها الطبيعية .

ميزة هذا الدواء عن السابق أن له تأثير سريع جداً ونفطيع الـ acute stage

وغالبية الناس تشعر بتحسن من أول جرعة (80%) ، ولكننا لا نستخدمه كوقاية prophylaxis

لنفس السبب الذي تم ذكره سابقاً ..

عندما يسبب هذا الدواء B₁ في الـ brain أحياناً يسبب أيضاً نفس الـ receptor

في الـ coronary a. ← receptor coronary VC وهذا قد يضر مرضى الـ ischemic disease

وأيضاً مرضى الـ angina (وهذا العيب لهذا الدواء) .

prophylaxis :-

1. propranolol (B blocker)
2. CCBs (calcium channal blockers
3. TCA (Try cyclic antidepression)
4. clonidine

Ergometrine :-

in uterus → ① VC for spiral Bvs (Bvs of uterus)
② direct spasm in uterus

- Uses :-

← يصبح إستخدامه في حالة الولادة (لأجل زيادة الطلق) ؟!

* لأنه يقوم بفعل: Contraction for uterus & servix

لكن: يستخدم جداً بإعطائه بعد الولادة (بعد خروج الـ placenta)
لأن الـ Contraction تساعد على التخفيف من النزيف بعد الولادة ...

Dihydroergotoxin :-

α blocker drug → VD (specially in the brain)

Use:- Senile cerebral insufficiency → الدم لا يصل للدماغ بشكل كافي
وبالتالي يسبب النسيان ، لذلك نستخدمه لمرضى الكبار في السن إذا كانوا يعانون من نسيان مستمر

Bromocryptine :-

(Stim. D receptor) :-

[1] hyper prolactenemia :- pituitry gland في الـ D يشبه الدواء مستقبلات
وهذا يسبب ↓ prolactine فنستخدمه لعلاج الحالات التالية :-

- Infertility - hyperprolactemia - stoppage for Lactation

[2] parkinson disease :-

(basal ganglia) عندما يقل الـ Dopamine في الدماغ يقل ، وتحديداً في الـ
يبدأ الشخص بالشعور بأعراض المرض والحل : لا نعطي الشخص هذا Dopamine
لأنه Bromocyptin الأفضل ، doesn't pass BBB أن نعطيه دواء الـ
لأنه non-catecholamine فبالتالي يستطيع الدواء المرور من الـ BBB
فيعمل بديلاً للـ Dopamine ويشبه D receptor وهذا مفيد لطريقة الـ parkinson dis.

* Adverse effect :-

1. ∩ & V
2. V.C in finger & Coronary a. ⇒ gangren + chest pain
3. Apportion → لأننا لا نستطيع ضمان الـ selectivity لأي دواء

Beta adrenergic ~~receptor~~ blockers :-

1. $B_1 + B_2$ → non selective e.g: - propranolol . . Sotalol . Timolol
   B_1 → e.g: - Atenolol . Bisoprolol . Timolol - Acetolol

2. BB + DVD action (Beta blocker with direct VD action)

عندما نُعطي المريض BB فإنها تقوم بفعل B_1, B_2 receptors ومن المعروف أن B_2 تتواجد بكثرة في الـ B_2 & Sk.m فيحدث VD ويبدأ المريض بالشكوى من :-

* prephral ischemia * problems due to blood flow for muscle

وهذا يُعتبر الفرق الأساسي بينها وبين مجموعة جديدة من الـ BB ← BB + DVD action

* Drugs :-

① Carvedelol ② Labetalol

* pharmacokinatics :-

→ selectivity :- ~~a~~ features :-

1- well absorped ② extensive 1st pass metabolism

→ Kinatics :-

a- Lipophylic : propranolol b- hydrophylic : atenolol

Lipophylic ← يعني أن هذا الدواء يذوب في الدهون وبالتالي امتصاصه يكون أفضل (شبه Compelet) لكن المشكل وأنه عند دخوله للجسم ينتشر بشكل جيد جداً ويوصل الـ CNS وغالباً يكون مسبوق بـ CNS effects لأنه يمر من خلال BBB لكن مشكلته في الـ metabolism لأنه يدخل للجسم كونه Lipid soluble وبالتالي يصعب على الـ Kidney إخراجه (excreted) water soluble إذ لابد له أن يمر على الـ Liver ويتحول له metabolism حتى يكون طارد وبالتالي هذا الأدوية تكون الـ (half - life) لها صغيرة .. ⁉ (Long duration of action = Long half-life) ← hydrophylic .. water soluble لأن الكبد يقوم بتكسيرها أيضاً أساساً

hypo	hydro
1- propranolol	1- Atenolol
2- its absorption better than hydro abs.	2- Less abs. than hypo .
3- reach → CNS	3- Dosn't Reach CNS
4- Extensive metabolism in Liver to be excreted to convert it to water soluble	4- Direct metabolism because it's : water soluble
5- Short duration of action	5- Long duration of action
6- ~~g~~ Multible dose	6- Once/day

* pharmacological affects :-

1- Heart :- B_1 receptor which ↑ all cardiac properties so if its block :-
↓HR , ↓ contractility , ↓ arrhythmia , etc
→ if ↑ it may lead to MI depression .

2- Blood vessels :-
B_2 (sk. m) → V.D
B_2 (coronary a.) → V.D

3- Blood pressure :- ↓ Bp :-
a- ↓ Cop b- ↓ Renin c- ↓ central sym. outflow
d- Resetting of paroreceptors e- Release for NO , PGI_2E_2

4- bronchi :- B_2 receptor → broncho dilatation

5- eye :- Glucoma .

6- CNS :- ⓐ ↓ NA ⓑ antidepresent
* if NA ↓ :- cause :-
- sedation - antianaxity - depression - nightmares ...

7- Tremors :- it may be (over activity of B_2)

Contra Indication :- with bronchial asthma pt.

* BB with special effects :-
[1] propranolol → non-selective + MSA (membrane stabelizing action)
= Local anathetic action

[2] pindolol → partial agonist (not 100 % blockers)

[3] EsmoLol → BB (very short duration) * it use in emergency

[4] LabetaLol :- Compind (α & β) blockers BB + DVD active
pheochromocytoma
يستخدم لعلاج :- ← تقلل وظيفة من فشل ال

Carvedolol :- BB, , non-selective

* antioxidant drug

Nebivolo :- . The most selective BB

. VD ⇒ secret NO so we count it (BB with DVD action)

- Uses :-

1- pt. with hypertension 2- IHD (ischemic heart disease) classic angina

3- S.V.T (supra ventricular tachycardia) 4- hyperthyrodism

5- Esophageal varix 6- Glucoma

7- ~~pheno~~ 7- pheochromocytoma.

- Adverse effect :-

1] fatgue :- ↓ cop ↓ Blood → sk.m * most common

2] Bronchoconstriction → never given to bronchial asthma pt.

3] Bradycardia → may lead to Heart block

4] ↑ prephral ischemia

5] Metabolic adverse effect :-

a- BB ↑ K in blood ⇒ not good for Renal failure pt.

b- ↑ plasma Lipids (↑C , ↑TG)

6] D.M

7] CNS :- * Depression * nightmare * sexual disfunction.

- Contraindication :- Absolute contraindication [Abs CI]

1] Bronchial asthma 2] Heart block

3] prinzymetal angina 4] if the pt. use it for long time [no sudden stopping]

- Not good :-

1] HF

2] P.V.D (prephral vascular disease)

3] D.M

4] athletic ⇒ fatigue

Adrenergic neuron blockers :- كل الأدوية اللي تشتغل على الـ nerve ending

*Drugs :

① α-M dopa :- * synthetic

* MOA :- participate in NA synthese → as a false substrate instate of formation of Dopamine from the normal Dopa ...

Useful for pregnant women. * حتى انه يُعتبر أفضل خيار لعلاج الـ hypertension في النساء الحوامل

* SE :-

- Depression - nightmare - Extrapyramidal Manifestation
- Hemolytic anemia - Autommune hepatetis
- Salt & water retention

* قد يحدث بعض التورم في بعض الحالات ثم إستخدامه لفترة طويل ، وهنا يجب إعطاء [mild diuretic] ويواصل علاج الضغط بصورة طبيعية ..

Reserpine :- NA , Dopamine , Serotonine

① ↓ Bp ② Depression ③ parkinsonism ④ hyper prolactemia

⇒ Used for # :- mild & moderate hypertension * لكنه ليس خيار الأول

- MOA :-

الآلية قائمة على أن الـ NA التي خرجت لتعمل وظيفة ما ثم حدث له reuptake فتقوم بمنع هذا الشيء وإيقاف رجوعها إلى الـ vessels وبالتالي تتراكم في الـ cytoplasm ويكسره بـ MAO !

* MAO inhibitor + Reserpine ⇒ Acute hypertensive crises .

Ach placeses :-

1- nerve ending 2- sk.m 3. CNS ganglia ...

* Cholienergic receptor :-

A- Nicotinic receptor [sk.m , ganglia , SRG]

N_1	N_2	N_3	N_n	N_m
- Gq - Exetitory - gastric	- ↓CAMP - inhibitor - Cardiac pt may lead to bradycardia	Gq exitory 1. Bvs 2- smooth m. 3- any gland 4- eye → (mydriasis)	ganglia	sk.m muscle contraction

* Drugs :-

M	N
- Carbacol	- Lobiline
- Bethanecol	- Nicotin
- Pillocarpine	

1) Carbacol :-

- stim M+N
- no chf → long duration
- don't give is systemic (local eye drop)

2) Bethanecol :

1- stim. M first mostly in git, urinary (specially M3)

* ↑ motility
* open sphincters

-> لذلك هناك خطورة تكمن في تأثير ال M2 على القلب بشكل سبب

1- Bradycardia 2- not good for pt. with (Retension) due to organic obstructure

3) pilocarpine

muscarinenic agonist

* شغال عالM3 بالأكثر

- ↑↑↑ secretions
- sgören syndrome : Dryness of all body secretion.
- eye drop → myosis

* SE :

D → Diarrhea
U → Urination
M → Miosis
B → Bradycardia, bronchoconstriction
L → Lacrimation
E → Emesis = vomitting
S → Salivation, sk.m twitches

* Contraindication :-

- Bronchial asthma (BA)
- Urine retention due to organic obstruction

Nicotenic agonist :-

1- Nicotin :- in small dose → stim. ganglia
in large dose → xx Ganglic
↓ CNS : * Depression for all physiological function of the body

B.Vs : ↑ symp. ganglia → V.C → ↑Bp

SRG : Stress → Adrenaline → V.C

pitutry gland → vasopricine (ADH) → V.C

2 Varecline : partial agonist
* لصفة تشبه النيكوتين
تستخدم لمساعدة المرضى للإقلاع عن التدخين

* Contraindication :- In pregnancy !

Indirect drugs :-
" Cholineasterase "
الأدوية اللي توقف عمل الـ ChE وبالتالي accumulation for Ach : يحدث
Ach ← يقوم الـ drug :- بالتأثير المطلوب بدلاً من الـ

Reversible
- Carburetion of the enz.
- Drugs :
1- physostigmine
2- Neostigmine
3- pyredostigmine
4- Edruphonium
5- Donepysine
* - Rivastigmine

Irreversible
- phosphorelation

physostigmine	Neostigmine
- plant	- synthetic
-N-	-N-
- stable	- unstable
- abs. well	- less abs.
- ✓ BBB	- ✗ BBB
- muscarenic effect	
- Nicotenic effect	
- CNS effect	
- Locally "eye drop" → Glucoma	
- urine retention	

* أقوى دواء يقوم بتأثير الـ miosis على العين هو Physostigmine

[3] M.G

- autoimmune disease.
- Neostigmine + Atropine ؟!

↑ muscle contraction ← stim. N_m receptor ← ↑Ach ← neostigmine نعطي الـ
to block unwanted mascarenic effect ← Atropine نعطي الـ

pyridostigmine :-
- more selective
- Long duration of action (5-6 h.)

Q:- Why [pyridostigmine] is preferred to ## M.G?
① more selective on muscular junction (without severe muscarenic effect)
② Long duration of action → (2ر3 daily)

[4] Edruphonia :
more selective (better than pyridostigmine)
لكن لديه عيب وهو أنه حين تم تصنيعه تركزوا على جعله (very selective) وبالتالي أصبح شغله يقتصر على الـ motor en plate وهذا سبب أن الدواء يخرج بسرعة من الجسم ولا يستمر تأثيره لأكثر من ٥-١٠ دقائق، لذلك لا يُستخدم هذا الدواء لعلاج العلاج وإنما التشخيص
→ cholinergic rise

[5] Donepezal, Rivastigmine :-
→ block ChE
→ no prephral effects
→ Alzheimer disease

* Irriversible :- organophosphase
→ Insecticides
→ Nerve gases

↑ Ach :-
- Cardiovascular sys. : bradycardia, hypotension
- Respiratory sys. : ↓↓ inherited
- GIT : Diarrhea, urination
- eye : severe myosis
- Sk. m : sweeting, twitches, salivation, Lactation.

H :-

A	B	C
air way	Breathing	circulation
suction	جهاز التنفس الصناعي	- pulse (severe bradycardia)
		- Bp (very low)

Drugs :-

1. Atropine (high dose) : Ampule 2 mg
   تعطيه للمريض كل خمس دقائق مع ملاحظة الـ pulse, Bp ويظل المريض تحت المراقبة ٤٨ ساعة
2. Oxime : - pralidoxime (PAM)
   - diacytylmonoxime (DAM)] CHE reactivator
   → given parentral I.v diffusion
3. Diazepam.

Date:
No:

First lecture... [GIT]

د/عبد المتعال خوده

- Peptic ulcer include → ulcer in stomach which called Gastric ulcer
  → ulcer in duodenum which called duodenal ulcer

- Peptic ulcer occures when there is impalance between the invasive and defence mechanisms
- Any defect ~~cause~~ in the defence force or increased in the invasive force causes ulcer.

The invasive forces	The Defence forces
* Hcl	* mucus Coat.
* Pepsin	* Bicarbonate
* NSAIDs	* Good Blood Flow.
* Smoking	
* H. Pylori	- Note \ Ischemia in the mucosa of the stomach may Caese Peptic ulcer.

- The mucosa of the stomach is Lined By \
  (1) ~~Peptic~~ Parietal cells ⇒ Secrets Hcl.
  (2) Cheif cells ⇒ Secrets Pepsin.
  (3) G cells ⇒ Secrets Gastrin [In stomach, Duodenum, pancreas]
  (4) Enterochromaffin cells ⇒ Secrete histamin

* histamine is the main stimulant of parietal cell to Secrete Hcl.

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* Parietal cells have 4 Receptors in their walls \
- M_1 receptor , G_1 receptor , H_2 receptor ⇒
Stimulation of these ↑ Secretion of Hcl.
- PG receptor ⇒
Stimulation of it inhibits the Hcl secretion.

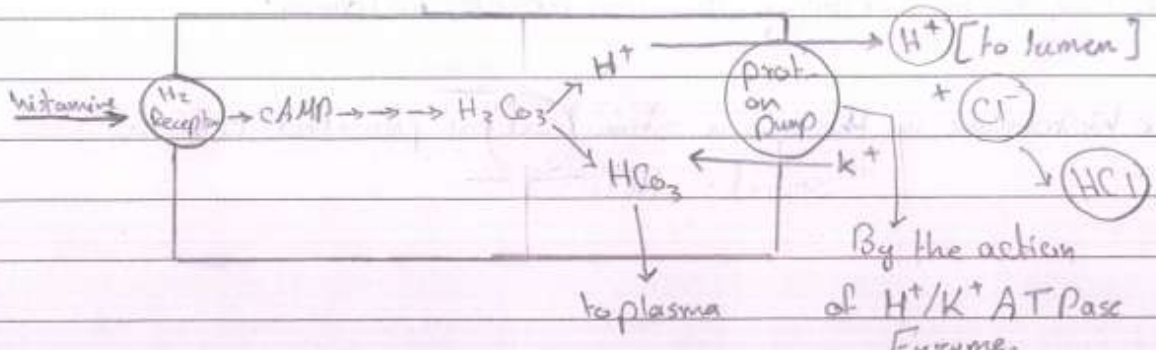
1] M_1 Receptor :-
- Stimulated By the action of acetylcholin under the effect of Vagal Tone.

* Note Ach stimulate also G cell to Secrete Gastrin and enterochromaffien cell to secrete histamine.

2] G Receptor :-
- Stimulated By Gastrin which is secreted under the effect of Ach stimulation on G cells.

3] H_2 receptor :-
- Stimulated By histamine which is secreted under the effect of Ach stimulation on enterochromaffien cells.

* Mechanism of formation of Hcl under the effect of histamin stimulation \



Date:
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4] PG receptor :-

- Stimulated By PGE_1 ⇒ Decreasing the formation of HCl and producing thick mucus coat also cause VD leading to increase Blood flow to the stomach.

---

* Mechanisms of decrease the Secretion of HCl :

1. Block M_1 receptors
2. Block G_1 receptors } « most minimal effect »
3. Block H_2 receptors ⇒ « the final pathway, very effective »
4. PG analoge
5. Protein Pump inhibitors ⇒ « The most effective drugs »

« H. pylori »

* Mainly found in the antrum, It hides Between the mucosal layer of the stomach and the mucus coat.

* It Secrete proteolytic enzymes causing chronic Gastritis which may develop into ulcer.
* Detected By urea breath test.
- 50% of pateints with H. pylori don't suffer from ulcer. only 10% of them may have ulcer.

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* Signs of P.U\

- mainly Epigastric pain.
- يجب أن تفرق إذا كان هذا الألم سببه P.U أم Cardiac
إذا كان هذا الألم مصاحب لأعراض هضمية ومنسبب Cardiac
وإن كان مصاحباً لتناول الأكل فهو P.U
وإذا كان مرتبط بحركة معينة فقد يكون السبب musculoskeletal .

* Difference Between GU and DU\

GU	DU
- Diffuse pain	- Localized pain + point tenderness
- May increase with eating + mostly	- Some times the pain Decrease after eating.

* The size of most ulcers is 1 - 2 cm , If it is more than 2 cm It is called Giant Ulcer and It need Surgery.

* Treatment\

- first the non pharmalogical treatment.

① Devoid the 3 S's.
Smoking , Stress , Spices and fried food.
+ Sedative عشان يقلل التوتر

② Stop the NSAIDs
* لكن لأحيان ممكن نخفف الجرعة.

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- Second the pharmacological treatment \

① Neutrilization of HCl = Antacids

② Anti-Secretory of HCl
- Block M_1 receptor
- Block M_2 receptor
- Proton pump inhibitors

③ Mucosal Defence Mechanism
- Sucralfate
- Bismuth Subsalicylate
- Carbenoxolol
- PG analog.

④ H. pylori treatment.

- First \ Neutralizing HCl = Antacids \ [= symptomatic relif]

① Na-Bicarbonate :-	② Ca-Carbonate :-	③ Mg and Al-Salts :-
* The fastest in action. * It can Be absorped and Reach the Systemic Circulation → lead to ↑ Sodium in the Blood causing By that Salt and water retention and Systemic alkalosis. - CI \ In hypotensive patients.	* 50% of it will absorped and ↑ calcium level in the systemic circulation * This may lead to Ca-stone formation. * If the dose was high, it will stimulate Gastrin Secretion * Also cause Rebound hyperacidity.	* Non. absorped 100% act locally. * But these salts will retain in the GIT and Cause: Mg ⇒ Diarrhea. Al ⇒ Constipation.

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- General Adverse effects of Antacids :-

* Change in Bowl hapittes [due to Mg, Al actions]
* May cause Rebound hyperacidity.
* Lead to cation overload :-
  1] Na ⇒ Salt and water retention
  2] Ca ⇒ ↑Ca ⇒ Ca stones
  3] Mg ⇒ ↑Mg, muscle fatigue ⇒ (إذا كان في فشل كلوي يتم تجنب Mg لأنه يتراكم)

* Formation of chemical complexes with other drugs [chelation] ⇒ (لذلك يفضل بين تناول الأدوية لمدة ساعتين على الأقل)

- Second Anti-Secretory drugs \

① M_1 Blocker :-
- Like ⇒ Pirenzepine
* Not very effective
* If the dose was high it may lose its selectivity and decrease the motility so much decreasing By that the time of empting ⇒ Lead to ↑ Hcl.

② H_2 Blocker :-
- Like ⇒ Cimeticline, Ranticline, famoticline and Nizaticline.
* ↓ Hcl By 70 %
* Clinical uses :- ① All types of ulcers
② with NSAIDs.
③ Zollinger-Ellison Syndrome

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- Zollinger-Ellison Syndrom Is a tumor of the G-cells in pancrease ⟹ Lead to increase Gastrin Secretion ⟹ ↑ HCl.

* Side Effects \

① Cimetidine ⟹ has ① Antiandrogenic Side Effects.

- Antiandrogenic effects include Gynecomastia, ↓ Sperm count, Galactouria, ↑ prolactin « endocrinal S.E. »

Causes drugs interaction ⟸ ② Inhibition of liver metabolism By Cytochrome P_{450}

③ Reversible hepatitis and Bone marrow depression

④ CNS effect ⟹ headach, Psychiatric ... [appere in old patient]

* يفضل أن لا تؤخذ هذه الأدوية الحوامل.
* لا يصرف مع أدوية أخرى لتأثيرها على P_{450}.
* جميع الأدوية التي تستخدم لـ HCl لا يتم إيقافها بشكل مفاجئ أبداً.

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	Cimeticline	Ranitidine	Famotidine
- Anticandrogenic	✓	X	X
- CNS effect	✓	±	X
- H_2 Blocking potency	-	+	+ +
- Duration of Action	3 times daily	2 times daily	Once daily
- Duration of treatment	6 weeks	6 weeks	6 weeks

* إذا كانت حالة المريض تحتاج استخدامهم لمدة 6 شهور بنحط الجرعة وقت النوم

Date:
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Third Proton Pump inhibitors

- like ⇒ ① Omeprazole ② Lansoprazole ③ Pantoprazole

* MOA :

- Inhibition of K^+/Na ATPase enzyme irreversibly

- has long duration of Action
- all of these drugs are prodrugs [must be activated By the HCl] inside the gastric Gland only.
- The most potient drugs, And used for 4 week then 4 months.

* C.I : Same as H_2 Blocker

* S.E :

① Diarrhea

② Inhibits Secretion of intrinsic factor [↓ absorption of B12]

③ Bioavilability changes for other drugs. [Due to change in stomach acidity]

④ omeprazole only inhibits the P_{450} So it has drug interaction with Clopidogrel. By inhibiting its activation in liver.

⑤ Osteoprosis [Ca need Hcl to be absorbed]

Date:
No:

Fourth Mucosal Defence Mechanism)

-like ⇒ Sucralfate compounds , Bismuth compounds, PG analog.

* MOA :

① Sucralfate ⇒ " Sulfated sucrose + Aluminium "

- Covers the ulcer and protect it.
- less than 5% will be absorped ⇒ Aluminium accomulates in Renal tissue , So It is C.I. for renal failuler patients.
- Sucralfate is activated By HCl and it act By Binding to the protein of the ulcerated tissue.
- By its Action it lead to ⇒ ↓ pepsin secretion and ↑ PG , preventing the irritation of H^+ and Hcl.

* لا يوصف مع PPI لأنه لا يشتغل بدون HCl

- Safe in pregnancy.
- The most common side effect is Constipation due to (Al)

② Bismuth Compound ⇒

- MOA same as Sucralfate.
- help in H.Pylori eradication.
- Some of it will absorped ⇒ Pass BBB ⇒ Causes encephalopathy.

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(3) Carbaxolol :-

* MOA :-
  - Stimulate mucus production from the healthy cells
  - ↑ healing of the ulcer due to ↑ Blood flow
  - ↑ rate of epithelial turn over.
* S.E :-
  - May cause salt and water retention
* C.I :-
  - In edema and hypertensive patients

- If edema occure due to this drug ⇒ Give any diuretic
  Except ⇒ Spirolactone Because it has steriodal structure [prevent competition Between them]

(4) Misoprostol :-

* MOA :-
  - Stimulate PG receptors on parietal cell
    ⇒ ↓cAMP ⇒ ↓ HCl production
  - Stimulation of mucus secretion.
  - Cause local V.D ⇒ ↑ Blood flow.
* S.E :-
  - Diarrhea due to ↑ mucous and water secretion
* C.I :-
  - In pregnancy ⇒ lead to uterine contractions.

Date:
No:

[H. pylori]

* Protocol of treatment for 10 or 14 days
By ⇒ P-CAT

1. PPI
2. Clarithromycin
3. Amoxicillin
4. Tinidazol.

Date:
No:

- Seccuel lecture [GERD] د/عبدالله جوده

« Gastroesophageal Relux Disease »

- It is the reflux of Gastric content and acid to the esophagus clue to incompetance ⇒ which may lead to reflux Esophagitis and transformation to columnar epi.

* Causes \
① Diabetes milletus.
② Pregnancy
③ Some drugs and disease.

* Symptoms \
- mainly morning heart burn

* Treatment \
① Life style modification.
② Drugs
③ In Sever cases ⇒ Surgrey

* تغيير في انماط الحياة وذلك برفع مقدمة السرير حوالي 20cm ومتابعة الرياضة وتجنب جميع مهيجات المعدة والابتعاد عن الاكل قبل النوم

Date:
No:

* Drugs \

First ↓ HCl By :-

① H_2 Blocker ② PPI

* The best antacid for this patient is Gaviscon which contain :-
  - Algenic acid
  - NaH_2Co_3
  - Mg Triselecate
  - $Al(OH)_3$.

Second Prokinetics drugs :-

Drugs which Increase the motility and enhanced evacuation By acting on the upper GIT.

[Drugs which work on the lower GIT are laxatives]

1] 5HT4 agonists \

* Mosaprite * Cisaprite * Rinxaprite

MOA ⇒ - Stimulat Serotonin Receptor type 4,
[found in GIT and heart]
- Increase Ach in upper GIT ⇒ ↑ motility.

- It may act on 5HT-4 receptor in the heart and cause ↑ Q-T interval [torsadogenic]

2] Bethanechole \

- MOA ⇒ work on M_3.
- Causing diarrhea
Non-selective ← غير انتقائي

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3] Erythromycin \ [Antibiotic]

- MOA ⇒ act on motilin Receptor which found in the upper GIT lead to ↑ motility

- Used in emergency only [Its tolerance is very fast]

4] D_2 Receptor Blockers \

(1) Metaclopramide :

- MOA \ (1) Block D receptor [D_2 more]

- D receptors are under control of Sympathetic System So, stimulating them lead to ↓ motility and Blocking them ↑ motility

- Metaclopramide is Not Selective ⇒ It Blocks D receptors peripherally and Centrally or CNS.

(2) Stimulate 5HT-4 receptors ⇒ ↑ Ach ⇒ ↑ motility

[Its action on the heart is weak]

(3) has antiemetic effect By :

Blocking D_2 receptors of the vomiting center which is found in area postrema of M.O.

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* C.I \

① GERD — HCl قوي جداً ⇐ لأنه الرجوع إلى المريء وفي حرقة الاستلقاء لأنه Selective.

② Gastroparesis in D.M

Neuropathy ⇐ لبس ⇐ Stomach إلى أسفل.

③ Before endoscopy.

In emergency ⇒ evacuate stomach.

④ Before emergency surgery to prevent Aspiration Pneumonia.

⑤ As Antiemetic drug.

* S.E \

Blocks D_2 centrally in :-

① Basal Ganglia lead to :-

- Extrapyramidal manifestation :-

① Dystonia ⇒ abnormal facial expression Reversibly.

② Dyskinasia ⇒ " " " Irreversibly.

③ Akathesia

④ Parkinsonism

② Limbic System lead to :-

Altered emotions

③ Pituitry Gland lead to :-

↑ Prolactin.

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② Domperidone :- Don't pass BBB

- MOA \

① Block D_2 peripherally
② Don't act on $5HT_4$
③ It is also antiemetic

[Block D_2 in area postrema which is outside BBB]

S.E \ ↑ Q-T interval
[Torsadogenic]

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*Third lecture \ د/ عبد الله خوده..

[Hepatic encephalopathy and esophageal Varices.]

- Superior mesenteric vein joint the splenic vein forming Portal vein which contain most of Blood of the mesenteric area.

- Chronic liver diseases cause damage or decreasing in the Blood entery to the sinousoid which will cause Increase of Blood pressure in the portal vein.

- Normally the BP in the portal vein is ≦ 9 mmHg portal hypertension mean > 12 mmHg.

- In portal hypertension the Blood goes in other pathways, one of these pathways is Left Gastric vein, which has an astomosis with systemic veins at the lower end of esophagus.

- Increase in portal tention will lead to \
① Dilatation of venous plexus at the lower end of esophagus « Varices »

② Chemical Complications :-
- Some bacteria in the intestine work on proteins « fermintation » and producing NH_3 and other toxic substances like [GABA like] and [Benzodiapezine like mediators]
* These substances causes CNS depression.

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- Patients with chronic liver disease ⇒ Their Blood can't be detoxified in liver, So the Blood shunts to other pathways with these Substances ⇒ Reaching Systemic circulation and to the CNS at the end.

* CNS effects of these Substances :-
  1. NH_3 ⇒ Brain edema
  2. GABA like ⇒ CNS Depression
  3. Benzodiapexine like mediator ⇒ CNS depression

- The Result is ⇒ hepatic Coma which is Called hepatic encephalopathy or portosystemic encephalopathy.

- So the major two complications of chronic liver disease are :
  1. hepatic encephelopathy
  2. esophageal varices.

* Note :- NH_3 ⇒ absorpable and cross BBB
  - NH_4 ⇒ ionized, can't be absorped and can't cross BBB.

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* Treatment of portosystemic encephalopathy \

1] low protein diet ⇒ Decreasing NH_3 production and replace it By vegetable proteins.

2] Lactulose ⇒ Not digestable sucrose, It dissolve inside the intestine into → Acetic Acid.
→ lactic acid.

- These acids will ↓ PH of the intestine which lead to :
① Bacterial will eradicated
⇒ lead to ↓ NH_3 production.
② NH_3 converted to NH_4 which is not absorped.
③ Shifting of NH_3 found in the Blood to the intestine.
④ Increase water inside intestine ⇒ lead to Intestine wash [laxative]

3] Antibiotic ⇒ locally work like :
① Neomycin
② Metronedazol
③ Refaximin

* Neomycin :- Not absorped, work locally
- In 1-2% of pateint, absorption will occure and enter to the systemic circulation causing By that ① Nephrotoxicity.
② Autotoxicity.

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* Metronedazol work on anaerobic Bacteria.

* Rifaximin Is an absorpable and work locally.

- These drugs are used as prevention from Complications.

Esophageal Varices

- These varices will cause Sever Bleeding so the treatment will Be as the following \

1. Fresh Blood transfusion.
2. The patient may develop stress ulcer so we give him PPI in I.V injection.
3. Give him any drug causing V.C in splancnic area Like "Vasopersin"

* Vasopersin act on V_1 receptors which are found in the mesenteric vascular bed, But it is not Selective, it will work on V receptors found in the cerebrum and kidney and heart which may cause Myocardial ischemia

* for myocardial ischemia give "Nitrate" ⇒ Act as Coronary vasodilator.

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* Vasopersin is not used any more, The isomer of it is Terpresin or Glypresin, It is more selective on Mesenteric vascular bed V.C and ↓ portal blood flow with out any Systemic vasoconstriction.

* also Octeatiet - Somatostatine ⇒ cause indirect Vasoconstriction

- These drugs will stop bleeding in 90% of patients

④ Endoscopic sclerotherapy
⑤ Transjugular intrahepatic porto systemic shunt [TIPSS surgery]

* Prophylactic Treatment:

1] Non Selective β-Blocker:- as propranelol.
- Used in high dose ⇒ ↓ Co ⇒ ↓ Blood flow to the MVB
- Indirect VC By Blocking B_2 receptors.
- [The patient will have sever fatigue]

2] Nitrate:
- Venous Dilatation ⇒ ↓ Venous return ⇒ ↓ CO ⇒ ↓ Blood flow to MVB.

3] Metoclopramid: to evacuta stomach faster.
4] PPI

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Fourth lecture \ د/عبدالله وهبي...

[Managment of constipation]

- Causes of Constipation :
  1. Chronic idiopathic constipation [CIC]
  2. pregnancy [the uterus compress on the intestine ↓ motility]
  3. Lack of motility
  4. Tumers

- Constipation is not serious condition only if this constipation is with sudden onset and the patient was ≥ 50 years, And Bleeding and wieght loss with history of colon cancer.

- Treatment :

* first \ Non pharmalogical treatment \
  - ↑ fibers in diet.
  - ↑ fluids
  - ↓ Coffee and Tea.
  - Exercise

  ⇒ 90% will treated if the cause wasn't obstructive.

* Second pharmalogical treatment \
  - Laxatives they increase the lower GIT motility and enhanced intestinal evacuation
  - Classification of laxative
    1. Bulk laxative
    2. Osmotic laxative
    3. Irritant laxative
    4. Lubricant laxative.
    5. chloride channel activator.

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1] Bulk laxative

① Bran ② Carboxymethyl cellulose ③ fibers.

* MOA :

It is not digestable substances ⇒ Causes Bulk inside the intestine ⇒ Distention in the mucosa of small intestine and colon ⇒ stimulate strech receptor ⇒ Local stimulation ⇒ ↑ motility and water Secretion.

* SE :

① abdominal bloating.
② ↳ digoxine absorption.
③ May cause intestinal obstruction

2] Osmotic laxative

① Epsom salts ② Lactulose ③ Polyethylene Glycol.

- Epsom salts used for rapid evacuation Not in CIC
- It is not digestable, Non absorbable
  ⇒ ↑ osmotic pressure inside the intestine ⇒ water secretion to the leumn.

* S.E :

- If there is injury or ulcer in the intestine may leud to absorption of :
  ① Mg ⇒ Arrythmias.
  ② Na ⇒ Na and water retention

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- Lactulose Acetic acid and lactic acid will ↑ osmotic pressure ⇒ water secretion to the lumen.

* SE:
abnormal discomforte

- polyethylene Glycol : the same.
* SE: hypokalemia

3] Irritant laxative
① Senna ② Castor oil ③ Bisacodyl

* MOA: Cause local inflammation or irritant to the mucosa and inhibits Na^+/K^+ ATPase
This lead to:
① Direct stimulation of the nerve plexus.
② ↑ local Secretion of water.

* SE:
① It is Not used in:
- Pregnancy ⇒ abortion
- lactating ⇒ Catharatic baby.
- Menstrual ⇒ ↑ Blood flow.
② In chronic use lead to: laxative habbite and catharatic colon.
③ Castro oil has bad taste.
④ Senna ⇒ Urine discoloration

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⑤ Bisacodyl ⇒ Sever Gastric irritant.

* So it is covered with substance which dissolve only in alkaline medium, So don't used it with antacid

4] lubricant laxative \

① Glycerin ② paraphenoid ③ Enema

- Glycerin hydroscopic material ⇒ stimulate water Secretion ⇒ lubrication of anal canal

- paraphin ∧ on digestable, Coating the fecal matter ⇒ Mucosa can't absorpe water from the fecal matter.

C.U ⇒ In Piles or anal fissures.

- enema for evacuation of the intestine.

5] choride channel activator \

*Lubiprostone [derivative of PGE$_1$]

- Used for CIC
- Act on CIC-cl channels which is found in the apical pole of the columnar cell ⇒ ↑ water Secretion.

SE ⇒ May cause ∧ausea and uncomfortable

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- So the General uses of laxatives \
  1. CIC
  2. X-Rays
  3. hepatic encephalopathy [lactulose]
  4. painful anal fissures and piles
  5. fastest the secretion of toxic substances.

- General G.I \
  1. Undiagnosed abdominal pain
  2. Organic obstruction

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